



Blind *Helicobacter pylori* Treatment in Dyspeptics in a High Prevalence Area

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ABSTRACT

Background: The initial management of dyspepsia is shifting away from the invasive endoscopic biopsy procedure to identify *H. pylori* before eradication treatment. A test-and-treat strategy is firmly in place, but choices can be limited in resource constrained environments.

Objective: To investigate the short term effect of blind eradication therapy in management of dyspeptic patients prior to knowledge of *H. pylori* infection status by serology and histology.

Patients: A cross sectional study of 125 consecutive patients presenting at a tertiary facility with dyspepsia were screened for other diseases and then offered blind triple *H. pylori* eradication therapy.

Methods: Participants underwent clinical evaluation and completion of a structured questionnaire eliciting sociodemographic, smoking and drinking habits and drug history. Stored sera were tested for liver transaminases, total protein, albumin, creatinine, urea, Hepatitis B surface antigen, Hepatitis C virus antibody and *H. pylori* IgG antibody by ELISA at the end of recruitment, while stool microscopy, occult blood test and abdominal ultrasound scan were done before upper gastrointestinal endoscopy, where antral biopsy specimens obtained were processed for *H. pylori* identification and histological assessment. Patients received oral amoxicillin 1g and clarithromycin 500mg twice daily or metronidazole 400mg three times daily (in place of clarithromycin) and omeprazole 20mg twice daily for fourteen days and came for follow-up at two and four weeks for assessment of treatment response. Data were entered into a computer and analysed using SPSS Version 16. Descriptive statistics, Chi-square test with Yates correction, t-test, ANOVA and the Cochran-Mantel Haenszel test to compare proportions of treatment success were used. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were determined. P values < 0.05 were considered significant.

Results: All patients (125) completed the study, 76 (60.8%) were females and the mean age of subjects was 35.3 ± 12.70 years (range 18 – 84); 74.4% of respondents were < 42 years of age and 90% < 55 years. *H. pylori* were detected by histology in 100 (80.0%) patients, 99 of whom were among the 117 (93.6%) positive by serology (Sensitivity 99%, PPV 84.6%, efficiency 84.9%). Endoscopy was normal in 5% of patients and gastritis 39.5%, oesophagitis 27.7%, and duodenitis 22.7%. The relationship between chronic gastritis inflammatory activity and *H. pylori* infection status was highly significant. Chi square $\chi^2 = 24.33$ $p = 0.000001$; Yates correction $\chi^2 = 20.04$ $p = 0.000008$. Symptom improvement was highly significant at both 2 and 4 weeks from baseline and between the two visits. ($p = .000$). Cochran-Mantel Haenszel test to compare proportions of treatment success by *H. pylori* status was highly significant ($Q = 112.067$ $p = .000$).

Conclusion: On a short term basis, blind empirical *H. pylori* eradication therapy is effective in the management of dyspeptic patients in a high prevalence area and can obviate the need for testing before treatment. Serology concurred very well with histology as a method of infection identification.

Key Words: Dyspepsia, *Helicobacter pylori*, High prevalence, Empirical treatment, Outcome

INTRODUCTION

Dyspepsia is a common and often bothersome symptom complex related to the upper gastrointestinal tract and has

an extensive differential diagnosis including gastroduodenal, oesophageal and biliary disorders among others. At presentation, patient symptoms tend to be multiple and do not reliably predict underlying causes or endoscopic findings.

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ISSN: 2231-2196 (Print)

ISSN: 0975-5241 (Online)

Received: 08.10.2019

Revised: 16.12.2019

Accepted: 12.01.2020

Pooled data from 99 studies put the global prevalence in the community at 20.8% with North European and American studies at 22% and Africa and South America, 35.7% and 37.7% respectively.¹ In Nigeria, a prevalence of 26% in a community-based study in northeastern² and 45% in the middle belt regions were noted over the same period.³ Chronic or recurrent dyspeptic symptoms have been reported in 20-30% of people in Britain^{4,5} and the incidence of the first time symptoms at 1% annually in the community.⁶ The wide variation in prevalence persists even when same diagnostic criteria are used.¹ Dyspepsia increases with age^{2,3} and is commoner in smokers, NSAID users and in females.¹

In the past, the need to identify the underlying cause of dyspepsia led to wide spread use of endoscopy where in the United Kingdom for instance, more than 1% of the population underwent gastroscopy each year.⁷ However, despite its high degree of diagnostic accuracy, qualitative systematic review does not support its effectiveness in managing dyspeptics, thus making generalized usage unrealistic.⁸

With the identification of *Helicobacter pylori* (*H. pylori*) as the most important aetiological agent of chronic active gastritis and peptic ulcer disease, and epidemiological causal relationship to gastric cancer and classification as a group 1 carcinogen⁹ a lot of progress has been made in detecting this organism in non-invasive ways in place of endoscopy in patients with upper gastrointestinal symptoms with the assurance that the subgroup with underlying ulcer disease could be cured and the risk of developing actual ulcer disease^{10,11} gastric cancer and lymphoma¹² removed in non-ulcer dyspepsia.

H. pylori as the most common chronic bacterial infection in humans¹³ affects 4.4 billion people worldwide according to pooled data from 62 countries.¹⁴ In Northern Europe and America, approximately one third of the population is affected¹⁵ but prevalence varies amongst ethnic groups, while more than 50% are infected¹⁵ in Eastern Europe, South America and Asia, and in Africa, 70.1%.¹⁴

Reported pooled prevalence of 87.7% is highest in Nigeria¹⁴ where rates in north are 58%, 69% and 91% in children <1 year, 7-10 years and 10-19 years respectively.¹⁶

Among dyspeptics in Nigeria, *H. pylori* seroprevalence of 94.5% was reported in the western region¹⁷ 81.5% on histology in the northwest¹⁸ and 91% by rapid urease test in the north central zone.¹⁹

Since the recognition of *H. pylori* as an infectious disease²⁰ in the 1980s and the demonstration of reliable non-invasive methods of detection, the test-and-treat method²¹ employing therapeutic strategies such as the triple therapy or Bazzoli triple therapy²² in environments where high susceptibility to metronidazole and clarithromycin or high eradication rates still exist, and the non-bismuth (concomitant) or traditional

bismuth based quadruple therapy for 14 days has been fully established as the standard methods of eradication. As about 20% of those with *H. pylori* infection will experience an *H. pylori*-related clinical disease²³ this strategy can reduce the numerous cases of non-ulcer dyspepsia and peptic ulcer related admissions and more than 100,000 surgical procedures each year²⁴ and also mitigate the risk of MALT, and gastric cancer²⁵ which annually causes over 738,000 deaths worldwide.²⁶

While the 2010 Maastricht Consensus Conference advocated the test-and-treat strategy for uninvestigated dyspepsia in populations with *H. pylori* prevalence greater than 20%²⁷ the implementation of such recommendations can be daunting in resource constrained settings. To keep our costs down, we set out to explore the symptomatic outcome of blind *H. pylori* eradication therapy in our dyspeptic patients whose status of infection were yet unknown.

Study design

This was a cross sectional study carried out at the Gastroenterology Unit of the Department of Medicine, University of Maiduguri Teaching Hospital (UMTH)²⁸ where 125 consecutive patients aged 18 to 84 years with symptoms of dyspepsia regardless of presence of alarm symptoms were enrolled after clinical evaluation and completion of a structured questionnaire eliciting sociodemographic, smoking and drinking habits and drug history. Subjects with chronic illnesses, or on antibiotics, non-steroidal anti-inflammatory agents (NSAIDs), steroids, bismuth, and proton pump inhibitors in the preceding one month were excluded.

Ethical clearance was obtained from the UMTH Ethical Committee and informed consent from participants. Stool microscopy, occult blood test and abdominal ultrasound scan to exclude diseases mimicking dyspepsia were done before they underwent upper gastrointestinal endoscopy according to standard procedures. Antral biopsy specimens were processed for *H. pylori* identification and histological assessment for severity of gastritis in accordance with the updated Sydney classification.²⁹

The sera from patients were tested for liver transaminases, total protein, albumin, creatinine and urea and remainder frozen at minus 20°C until analysis was carried out for *H. pylori* IgG antibody (Immunolisa Tm Quantitative Organics, Israel), Hepatitis B surface antigen (Antec Diagnostics, United Kingdom) and Hepatitis C virus antibody (rapid chromatographic immunoassay for qualitative antibody detection).

After endoscopy all the patients received oral *H. pylori* eradication therapy consisting of amoxicillin 1g and clarithromycin 500mg twice daily, or metronidazole 400mg three times daily (in place of clarithromycin) and omeprazole

20mg twice daily for two weeks. None of the investigators or the patients had prior knowledge of *H. pylori* status at the time of treatment initiation. The participants were asked to come for follow-up at two and four weeks, at which visited patients were asked about the dyspeptic symptoms, while epigastric tenderness was elicited; “worse,” “same,” “improved”, and “much improved” (Likert-type scale) were used as measures of response to treatment. Other outcome measures included the presence of *H. pylori* antibody and bacteria on antral biopsy.

The data obtained were entered in to a computer and analysed using SPSS Version 16 Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics and where appropriate, additional analyses with Chi-square with Yates correction, t-test, ANOVA and the Cochran-Mantel Haenszel test to compare proportions of treatment success and by *H. pylori* status were used. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were determined. P values < 0.05 were considered significant.

RESULTS

All patients (125) completed the study, 76 (60.8%) were females and the mean age of subjects was 35.3 ± 12.70 years (range 18 – 84); 74.4% of respondents were < 42 years of age and 90% < 55 years.

As previously reported, *H. pylori* was detected by histology in 100 (80.0%) patients, 99 of whom were among the 117 (93.6%) positive by serology.²⁸

Measures of validity for the serology test using histology as gold standard returned sensitivity, specificity, positive predictive value, negative predictive value and efficiency of 99%, 28%, 84.6%, 88.9% and 84.9% respectively.

Patient symptoms by *H. pylori* status is shown in Table 1. While chest pain, eructation, haematemesis and melaena were seen only in seropositives and none in those without infection, the differences were not statistically significant.

Table 1: Distribution of symptoms in study subjects by *H. pylori* serology

Symptoms	<i>H. pylori</i> positive (n = 117)	<i>H. pylori</i> negative (n = 8)	P-value
Chest pain	15	-	0.35*
Epigastric pain	117	8	-
Water brash	23	2	0.50*
Halitosis	15	2	0.26*
Nausea	16	1	0.70*
Eructation	3	-	0.82*
Haematemesis	6	-	0.67*
Melaena	14	-	0.37*

*Not significant

Antral gastritis was the commonest finding on endoscopy and no case of peptic ulcer was visualised during the period of study. (Table 2)

Table 2: Showing results of endoscopic findings

Endoscopic findings	Number	Percentage
Oesophagitis	35	27.7%
Gastritis	50	39.5%
Duodenitis	28	22.7%
Bile Reflux	5	4.2%
Hiatus hernia	1	0.8%
Normal	6	5.0%
Total	125	100%

The relationship between the degree of inflammatory activity in chronic gastritis and *H. pylori* infection status among our patients, was highly significant (p=.000). (Table 3)

Table 3: Relationship of Histological activity (Gastritis) and *H. pylori* serology status

Antral Histology	<i>H. pylori</i> status by Serology N (%)		Total N (%)	p-value
	Positive	Negative		
Normal	0 (0)	8 (6.4)	8 (6.4)	0.000001*
Mild	25 (20)	10 (8)	35 (28)	
Moderate	54 (43.2)	6 (4.8)	60 (48)	
Severe	21 (16.8)	1 (0.8)	22 (17.6)	
Total	100 (80)	25 (20)	125 (100)	

* Chi square $X^2 = 24.33$ p= 0.000001; Yates correction $X^2 = 20.04$ p=0.000008

Abnormalities on stool microscopy were noted in 17 (13.6%) of the patients and consisted of undigested food particles, starch or oil droplets in 14 patients and *Entamoeba histolytica* infection in 3, all in the seropositive group.

Occult blood test was positive in only 7 (5.6%) of the participants, but 50% of the 14 with history of melaena.

On abdominal ultrasound scanning, two patients in the infected group had abnormal gall bladder reports. One was enlarged with thickened wall and sludge, and the other, had stones.

Screening for HBsAg was positive in 15 (12%) while 8 (6.4%) had hepatitis C antibody detected and 2 (1.6%) dual infections, all in the *H. pylori* infected patients, but this did not attain statistical significance. One of the patients had hypoalbuminemia, but had no evidence of decompensated liver disease.

The clinical response to treatment which were significant at both 2 and 4 weeks follow up and statistical analysis are depicted below in Table 4 and Table 5.

Table 4: Clinical response to triple therapy *H. pylori* eradication at 2 and 4 weeks

Response to Triple therapy	<i>H. pylori</i> seropositive (P)		<i>H. pylori</i> seronegative (N)		All Patients (P+N)	
	2 weeks (%)	4 weeks (%)	2 weeks (%)	4 weeks (%)	2 weeks (%)	4 weeks (%)
Much improved	6 (5.1)	104 (88.9)	6 (75.0)	0	12 (9.6)	104 (83.2)
Improved	111 (94.8)	13 (11.1)	2 (25.0)	6 (75.0)	113 (90.4)	19 (15.2)
Same	0	0	0	2 (25.0)	0	2 (1.6)
Worse	0	0	0	0	0	0
Total	117	117	8	8	125	125

Table 5: Statistical analysis of patients' treatment responses at 2 and 4 weeks

Paired Responses	Mean	Standard Deviation	Stand Error Mean	95% Confidence Interval of the Difference		t	df	Significance (2-tailed)
				Lower	Upper			
P2Wks - Baseline	1.0513	.2215	.0205	1.0107	1.0918	51.333	116	.000*
P4Wks - Baseline	1.8889	.3156	.0292	1.8311	1.9467	64.734	116	.000*
P4Wks - P2Wks	.8376	.3704	.0342	.7698	.9054	24.460	116	.000*
N2Wks - Baseline	1.75000	.46291	.16366	1.36300	2.13700	10.693	7	.000*
N4Wks - Baseline	.75000	.46291	.16366	.36300	1.13700	4.583	7	.003*
A2Wks - Baseline	1.09600	.29578	.02646	1.04364	1.14836	41.429	124	.000*
A4Wks - Baseline	1.81600	.42850	.03833	1.74014	1.89186	47.383	124	.000*
A4Wks - A2Wks	.72000	.57642	.05156	.61796	.82204	13.965	124	.000*

P – Seropositive N – Seronegative A – All evaluable patients (P+N)

2Wks – 2 weeks 4Wks – 4 weeks *Significant

Reliability Statistics - Cochran-Mantel Haenszel test to compare proportions of treatment success and by *H. pylori* status:

Q=112.067 P=.000

DISCUSSION

This study returned the same serological and histological infection rates (94% and 84% respectively) reported 15 years earlier in the same environment³⁰ indicating possibly that the socioeconomic status of the inhabitants of the region characterized by low educational attainment, large number of inhabitants in a house and unemployment among other things¹⁸ may not have changed, thus supporting an Australian report asserting that troublesome gastrointestinal symptoms are linked to socioeconomic status, with more being reported by subjects in low socioeconomic class.³¹

The highest concentration of seropositives was seen among 28 to 42 years old (50%) and the lowest in the elderly (3.2%). Furthermore, 80% of the subjects were under 45 years, the age where organic disease in the gastrointestinal tract is said to be rare.³² Compared to the western world our patients were younger with 90% of the studied population under the sixth decade of life.

While this supports the finding that *H. pylori* is common in the third to fourth decades of life^{21,28} there was no statistically significant difference between the two groups, ($p > 0.05$). This differential age prevalence in our cohort supports the

suggestion that serology can be used for screening young dyspeptics, as inaccurate test results are said to be more common in the elderly.³³

Epigastric pain and tenderness as previously documented in the same community³⁴ as the commonest clinical features in the index population is in consonance with a report from Zaria³⁵ unlike nocturnal pain in Kano subjects.¹⁸ Patients who were *H. pylori* positive had more symptoms than those without, but this did not achieve statistical significance. While data from multicenter studies have suggested that age should be discountenanced in favour of alarm symptoms due to its poor predictability of underlying pathology³⁶ neither age nor alarm symptoms were predictive of underlying pathology in this study group which further supports the NICE recommendation that all dyspeptic patients without alarm symptoms irrespective of age should initially be managed without endoscopy.³⁷

As previously documented in this population, antral gastritis (37.6%) remains the most frequent finding³⁸ as against gastritis with duodenitis in some series.^{17,35} We found no endoscopic abnormalities in 5% of patients who belonged to the *H. pylori* negative group, which agrees with the 6% from Ife.³⁹ Our findings support the report that

systematic review of models using risk factors, history, and symptoms did not reliably distinguish between functional dyspepsia and organic disease⁴⁰ or severity of gastritis⁴¹ as all our cases could be categorized as non-ulcer dyspepsia, unlike a study in northwestern Nigeria which reported equal rates of non-ulcer dyspepsia and peptic ulcer disease (34.5% and 35% respectively), distantly followed by gastritis (9.9%).¹⁸

As previously highlighted as the African enigma, peptic ulceration is still lower in this population compared to the rate of *H. pylori* infection.³⁸ This is attributed to the strains of *H. pylori*⁴² and the lower basal acid and maximum acid outputs in asymptomatic African controls⁴³ compared to westerners, possibly due to the less pathogenic effect of *H. pylori* infection acquired in childhood than in adulthood as suggested by Graham.⁴⁴

Histology to a significant extent corroborated the validity of serology in detecting *H. pylori* in our patients not minding the possibility that prior antibiotic treatment or inadequate biopsies could have reduced the detection rate.

The degree of histological activity was more in those positive by either serology or histology or both attaining high statistical significance ($p < 0.000001$), thus comparable with studies utilizing ¹³C levels where the degree of histological gastritis corresponded to the number of *H. pylori* organisms.⁴⁵

Giardiasis which can be chronic and may not produce diarrhoea, and responds to metronidazole⁴⁶ has been suggested as an important differential in dyspepsia in Scottish children⁴⁷ was not detected in any of our patients.

Abdominal ultrasound scan is still important in evaluating dyspepsia as demonstrated in two patients positive for *H. pylori*, yet had gallbladder disease.

The reported presence of both HBV (13%) and HCV (6.8%) and dual (1.6%) infections occurring exclusively in the *H. pylori* serology positive subjects may just be a reflection of the trend in the population^{48,49} as there was no significant statistical relationship to the status of infection.

All the serologically positive patients at 2 weeks after *H. pylori* eradication therapy indicated improvement in symptoms with 5.1% showing much improvement. By 4 weeks, an even higher proportion (88.9%) had much improved ($p=.000$) which is the expected outcome of specific therapy.

Conversely, in the *H. pylori* negative group, all patients who reported initial improvement at 2 weeks had a decline in outcome at 4 weeks. The 6 subjects (75%) who reported much improvement declined to “improved” and the other 2 (25%) reverted to the “same” (status quo ante). This is the anticipated response when eradication therapy is used in non-*H. pylori* dyspepsia.

While this inferior response in the uninfected group supports the view that the empirical use of antibiotics without the confirmation of *H. pylori* is not recommended⁵⁰ the overwhelming (98.4%) response in our patients, (83.2% much improved and 15.2% improved) at 4 weeks strongly supports the empirical use of antibiotics; more so, they all received eradication therapy before their infection status were known. Only 2 (1.6%) of 125 patients at 4 weeks that reverted to *status quo ante* can be assumed to have inappropriately received eradication therapy.

Those who benefitted included patients with oesophagitis and reflux symptoms (gastric and biliary) though the beneficial effect of PPI related acid suppression in this group cannot be ruled out considering the short period of follow up.

If we depended solely on the gold standard test, the relief reported by 23 patients (17 histological and 6 of 8 serological) would have been denied them, thus supporting the suggestion that a response to eradication of *H. pylori* in 5–10% of all patients with non-ulcer dyspepsia would make screening and treatment for *H. pylori* a beneficial option, irrespective of any other potential benefits.⁵¹

Limitations of the study

Our study showed that all our patients could initially be started on eradication therapy and other approaches used if some showed no improvement, however, concerns still remain because of the possibility of delayed diagnosis of gastric cancer, 87 cases of which were reported in our hospital⁵² a referral tertiary institution over a 16-year period. Reports from other parts of Nigeria also indicate that gastric malignancies have been seen in the third and fourth decades in patients though they presented with complicated dyspeptic symptoms some lasting 12 months.⁵³ Even though endoscopy in all our patients removed intervention bias as may be seen in comparative studies of test-and-treat versus endoscopy and treatment⁵⁴ the possibility of patient satisfaction after detailed explanation of the procedure may have positively impacted treatment outcome in the short term.

In light of the reported resistance issues, it must be emphasized that the triple therapy we employed in our patients may no longer be appropriate as the antibiotic stewardship in Nigeria is suboptimal due to the high rate of over-the-counter availability of prescription-only medicines including antibiotics and antibiotic-containing triple therapy ulcer drugs.^{55,56}

The fear of empirical treatment increasing the problem of community-acquired antimicrobial resistance in view of the rather high inappropriate prescription rates in primary care practice in some countries⁵⁷ can be minimized if appropriate antibiotic stewardship is embraced.^{57,58}

CONCLUSION

H. pylori must be viewed as an infection which requires specific eradication therapy using appropriate regimen where susceptibility testing is available in dyspepsia management in view of the widespread resistance to clarithromycin and metronidazole reported in several regions of the world. Where it is not as is often the practice among gastroenterologists, empirical therapy must be based on usage of quadruple therapy, local bacterial resistance patterns and recommendations, and drug availability.

While it has been advocated that even in high prevalence areas there should be testing before treatment for *H. pylori* our study has conclusively shown that in high prevalence resource limited areas, blind *H. pylori* eradication is effective and feasible and can obviate the need for specific methods of *H. pylori* detection and endoscopy in most of our patients. Therefore, the suggested cost-effective approach to dyspepsia management in our population is: treat to eradicate, and if no improvement; give empirical PPIs, and lastly administer endoscopy as appropriate. We recognize however, that the management of dyspepsia should vary in different countries depending on the incidence of *H. pylori* infection and gastric cancer rates as cancers are commoner in some regions than others.

Conflict of Interest

The authors have no conflict of interest to declare

Funding

The study was partly funded by the University of Maiduguri Teaching Hospital, Maiduguri as grant for Dr. Aisha S. Adamu's fellowship dissertation preparation.

- Northeastern Nigeria remains a high prevalence area for *H. pylori* infection
- Serology concurred very well with histology as a method of infection identification.
- Blind *H. pylori* eradication therapy was effective in the management of dyspeptic patients
- The need for testing before treatment can be obviated in most of our patients

Glossary of Abbreviations

ANOVA – Analysis of variance

HBV – Hepatitis B virus

HCV – Hepatitis C virus

IgG – Immunoglobulin G

MALT – Mucosa associated lymphoid tissue

NICE – National Institute for Health and Care Excellence

NPV – Negative predictive value

PPV – Positive predictive value

SPSS – Statistical Package for Social Sciences

UMTH – University of Maiduguri Teaching Hospital

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